PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference BERK-017WO	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US03/13492	International filing date *(day/month/year)* 29 April 2003 (29.04.2003)	Priority date *(day/month/year)* 30 April 2002 (30.04.2002)
International Patent Classification (IPC) or national classification and IPC IPC(7): C12N 15/00, 15/09, 15/63, 15/70, 15/74 and US Cl.: 435/320.1		
Applicant THE REAGENTS OF THE UNIVERSITY OF CALIFORNIA		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of ___ sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
07 October 2003 (07.10.2003)	06 January 2005 (06.01.2005)
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Patricia A. Duffy Telephone No. 571-272-1600

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US03/13492

I. Basis of the report

1. With regard to the elements of the international application:*

☒ the international application as originally filed.

☒ the description:
pages 1-32 as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages 33-35, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the drawings:
pages 1-4, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the sequence listing part of the description:
pages 1-11, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☒ contained in the international application in printed form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE

☐ the claims, Nos. NONE

☐ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US03/13492

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The question whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 12-24

because:

☐ the said international application, or the said claim Nos. ____ relate to the following subject matter which does not require international preliminary examination *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 20-22 and 24 are so unclear that no meaningful opinion could be formed *(specify)*:

Improper multiple dependent claims not searched in 210

☐ the claims, or said claims Nos. ____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 12-24

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	3-5,10 and 11	YES
	Claims	1, 2 and 6-9	NO
Inventive Step (IS)	Claims	3-5, 10, 11,	YES
	Claims	1, 2 and 6-9	NO
Industrial Applicability (IA)	Claims	1-11	YES
	Claims	NONE	NO

2. CITATIONS AND EXPLANATIONS

Claims 1, 2 and 6-9 lack novelty under PCT Article 33(2) as being anticipated by Shen et al , (Proceedings of the National Academy of Sciences of the United States of America, 92(9):3987-3991, 1995).

Shen et al teach a plasmid integration vector capable of site specific *Listeria* genome integration (see page 3987, column 2, see plasmid construction, delivery to the *Listeria monocytogenes* genome) and how to make such using particular restriction endonucleases. The vector comprises a site-specific plasmid with a heterologous coding sequence and multiple cloning sites (i.e. as a derivative of pBR322). The vector was prepared using pBR322 as a base and thus necessarily possesses multiple cloning sites because pBR322 has multiple cloning sites. The vector was used to transform *Listeria monocytogenes* by electroporation, provide for culturing of the transformants expressing a heterologous polypeptide and used as a vaccine for a particular virus. As such, Shen et al destroys the novelty of the claimed invention.

Claims 3-5, 10 and 11 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest *Listeria* integration vectors using a listeriophage integrase or the claimed integration sites.

----------NEW CITATION(S)----------

SHEN et al. Recombinant Listeria monocytogenes as a live vaccine vehicle for the induction of protective anti-viral cell-mediated immunity. Proc. Natl. Acad. Sci., USA. April 1995, Volumn 92, Number 9, pages 3987-3991.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US03/13492

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

Please See Continuation Sheet

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

VIII. The following observations on the clarity of the claims, description, and drawings or on the questions are made:

Claims 1-9 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because the claims not fully supported by the description. The application, as originally filed, did not describe: the claimed invention.

The claims are drawn to Listeria integration vectors/plasmids. Vectors/plasmids are specific nucleic acid sequences whose structure must be described by way of the disclosure. The teachings of the disclosure are limited to two specific vectors, pPL1 and pPL2, with specific integration sites for *Listeria monocytogenes*. Neither the nucleic acid sequence of these sites (comK or tRNAarg) nor the full length plasmids are specifically disclosed. Even then, these specific integration vectors do not integrate with all strains of *Listeria monocytogenes* (see disclosure page 31, line 13 to page 32 line 2). The disclosure is devoid of nucleic acid sequence data for specific sequence integration sited for other species of Listeria. The disclosure or disclosure does not place any structure, chemical or functional limitations on the claimed vector. The recitation of "site-specific Listeria genome" does not convey a common structure or function. The scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The disclosure and the claims do not provide any guidance on the structure of the polypeptide and what changes can or can not be made. Structural features that could distinguish appropriate nucleic acids in the genus from others in the nucleic acid class are missing from the disclosure and the claims. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description, because specific, not general guidance is needed. Since the disclosure fails to describe the common attributes or structural characteristics that identify members of the genus, and because the genus is highly variant, the function of capable of site-specific Listeria genome integration alone is insufficient to describe the genus of vectors that function equivalently. One of skill in the art would reasonable conclude that the disclosure of a two specific vectors with two specific integration sites limited to *Listeria monocytogenes*, fails to provide a representative number of species of genome specific integrations sites in Listeria monocytogenes alone and does not provide for written description of genome specific integration sites in other Listeria species. Applicants were not in possession of the claimed genus because the disclosure does not convey to one of skill in the art a representative number of variants in structure and function of any such vectors that have the claimed/structure and function. The genus of vectors with the claimed function is substantial and highly variant because the vectors do not have a common structure and function. The recitation of "site specific Listeria genome integration" or the comK integration site or the tRNAarg integration site does not convey a common structure nor a common function. As such, generically sequences that are unrelated via structure and function are highly variant and not conveyed by way of written description by the disclosure at the time of filing. As such the disclosure lacks written description for the

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

highly variant genus of single function vectors with structurally undefined attachment sites, integration sites, genes which are not provided by the art.

Claims 1-9 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because of the claim not fully supported by the description. The description does not disclose the claimed invention in a manner sufficiently clear and complete for the claimed invention to be carried out by a person skilled in the art for the following reasons.
The claims are generically drawn to vectors capable of site-specific *Listeria* genome integration, *Listeria* transformed by the vectors, vaccines and kits for making vectors. These claims are not enabled for the following reasons. In order to provide for site-specific genome integration one must have a prior knowledge of the sequence of the Listeria genome, sequence of the bacteriophage/listeriophage attachment sites or the disclosure must describe such. It is noted that the disclosure does not describe these sites by way of nucleotide sequence structure for either *Listeria monocytogenes* or any other *Listeria* species. The disclosure does not point to the art where these sequences are described. Absent specific sequence information or structural definition, one skilled in the art would not know how to make site-specific *Listeria* genome integration vectors merely based on the functions of genome integration, bacteriophage attachment sites, comK and tRNAarg integration sites. Additionally, the disclosure lacks any information regarding vaccines, appropriate polypeptides, suitable protection studies in any relevant animal model using the *Listeria* cells of the invention. The vaccine art has long established that antigenicity does not correlation with protection from disease. As such, the disclosure does not teach how to make and use the invention as broadly claimed and it would require ingenuity far beyond the level of the skilled artisan and undue experimentation to make and use such vectors etc given the lack of specific nucleic acid structural information in the disclosure and in the art with respect to Listeria genomes, bacteriophage/listeriophage attachment sites and a comK or tRNAarg integration site.